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FORMULATION DEVELOPMENT OF OLMESARTAN MEDOXOMIL SOLID SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT Olmesartan medoxomil (OLM) is a novel selective angiotensin II receptor blocker USFDA approved drug for the treatment of hypertension. The oral bioavailability of OLM is 26% in healthy humans due to low solubility in water. The aim of the present investigation was to develop a self-microemulsifying drug delivery system (SMEDDS) to enhance the solubility of OLM. The screening study of OLM with different oils, surfactants and co-surfactants was done. Out of study optimized batch was converted in to solid freeze dried powder using 2% w/v mannitol as cryoprotcatant by lyophilization technique. This freeze dried powder shown good flow properties. The in vitro dissolution shown that about 99.28±0.013% of the drug is released within 45 min in freeze dried Solid-SMEDDS, while plain drug showed only 37.88±0.025% and marketed tablet shown only 58.31±0.015 % dissolution at the end of 45 min. The *in vitro* dissolution studies indicate that formulation of OLM in the form of freeze dried powder enhances the dissolution properties.

KEYWORDS : Olmesartan medoxomil, solid self-microemulsifying drug delivery system, enhance solubility

INTRODUCTION

In recent years, much attention has turned to lipid-based formulations with the aim of improving the oral bioavailability of poorly water soluble drugs. Lipid-based formulations encompass a diverse group of formulations, very different in physical appearance, ranging from a simple tri-glyceride vehicle to more sophisticated formulations such as Self emulsifying drug delivery systems (SEDDS).[1]S-SMEDDS, one of the lipid-based drug delivery systems prepared by the incorporation of liquid excipients into powders by solidification, is a promising drug delivery system for poorly water soluble compounds as it combines the advantages of liquid SMEDDS (solubility and bioavailability enhancement) with those of solid dosage forms (high stability with various dosage forms options).[2] S-SMEDDS produce oil-in-water microemulsions with droplet sizes of less than 200 nm upon mild agitation in aqueous media (such as gastrointestinal fluids). These fine microemulsion droplets have the advantage of presenting the drug in a dissolved form with a large interfacial surface area for drug absorption, which results in an enhanced and more uniform and reproducible bioavailability. Microemulsions help in the improvement of drug bioavailability**,** protection against enzymatic hydrolysis and decrease toxicity. The only problem with microemulsion is poor palatability and moreover due to their water content, microemulsions cannot be encapsulated in soft and hard gelatin. Hence, there is a need for delivery of lipophillic drug in S-SMEDDS. The self emulsifying formulations mostly will be in liquid or semisolid form due to the presence of large amount of lipids. Capsule filling is the one of the most economical and common techniques for the encapsulation of liquid or semisolid self emulsifying formulations for the oral route.

SPRAY DRYING

In this technique, formulation preparation involves by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixtures before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The volatile phase (e.g. the water contained in an emulsion) evaporates as the droplets introduced into a drying chamber, forming dry particles under controlled temperature and airflow conditions. Critical parameters of spray drying includes Inlet temperature of air, Outlet temperature of air, Viscosity, Solid content, Surface tension, Feed temperature, Volatility of solvent, Nozzle material. . According to the drying characteristics of the product and powder specification the atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are select

SPRAY COOLING

It also referred to as spray cooling, the process involves spraying molten formula into a cooling chamber and, upon contact with the cooling air, the molten droplets congeal and recrystallize into spherical solid particles that fall to the bottom of the chamber as fine powder. The fine powder may then be used for development of solid dosage forms such as tablets or capsules. Equipment like rotary, pressure, two-fluid or ultrasonic atomizers are available to atomize the liquid mixture and to generate droplets. Most of the recent research conducted on spray cooling with lipid-based excipients used ultrasonic atomizers. The main classes of excipient used with this technique are polyoxylg lycerides and, more specifically, stearoyl polyoxylg lycerides Gelucire® 50/13. The congealed particles are strong and nonporous as there is an absence of solvent evaporation. Ideally, the meltable materials should have defined melting points or narrow melting rang.

SOLID CARRIERS

In this technique the adsorbents (free flowing powder material) having good adsorption efficiency were used to adsorb the liquid self-emulsifying formulations on to it and converted into solid form.

This procedure involves two steps- The mixture is uniformly adsorbed by mixing in a blender. The obtained solid mixture is directly filled into capsules or by adding suitable excipients compressed into tablets.

MATERIAL AND METHOD

Evaluation of liquid SMEDDS formulation [4-7]

Dispersibility Test

The dispersibility test of SMEDDS is carried out to assess its capability to disperse into emulsion and the size of resulting globules to categorize them as SMEDDS. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). 1 ml of each formulation is added to 500 ml of water at 37 ± 0.5 °C and the paddle is rotated at 50 rpm. On titration with water the SMEDDS formulation forms a mixture or gel which is of different type (given in table 15) depending upon which the *in vitro* performance of formulation can be assessed

Robustness on dilution

Robustness to dilution was studied by diluting liquid SMEDDS formulation, 100 and 1000 times with various media like distilled water and 0.1 N HCl and checked out any phase separations or precipitation of drug even after 12 hrs of storage, that formulation is considered as robust to dilution.

Emulsification time[8]

The emulsification time was monitored by visually observing the disappearance of SMEDDS and the final appearance of the microemulsion in triplicate. A visual test to assess the self emulsification properties of SMEDDS formulation was performed by visual assessment as previously reported. In this method, a predetermined volume of formulation 1 ml was introduced into 300 ml of water in a glass beaker that was maintained at 37°C, and the contents mixed gently using a magnetic stirrer. The time to emulsify spontaneously and progress of emulsion droplets were observed.

Percentage Transmittance [9-10]

The percentage transmittance of the liquid SMEDDS after the 100 times dilution with distilled water measured at 650 nm using UV visible double beam spectrophotometer keeping water as blank.

Drug Content

OLM from SMEDDS formulation was extracted in methanol using sonication technique. The solutions were filtered, using Whatman filter paper. The methanolic extract was analyzed for the OLM content spectrophotometrically (UV-1800, Shimadzu, Japan) at 257 nm using standard curve.

In-vitro Dissolution Study

The quantitative *in vitro* dissolution studies are carried out to by dialysis bag method. The SMEDDS formulation was instilled in Dialysis beg equivalent to 20 mg OLM and one end was tied with thread and was placed in 900 ml of 0.1 N HCL as dissolution medium at 37±0.5˚C. The revolution speed of paddle was maintained at a rate of 100 rpm. Samples (5ml) were withdrawn at regular time intervals (0, 5, 10, 15, 20, 25, 30, 35, 40 and 45 min.) and aliquot amount of 0.1 N HCL was replaced. The samples were analyzed for the drug content using UV spectroscopic method at 257nm.

Thermodynamic stability studies [11]

The physical stability of a formulation is very important for its performance as it can be adversely affected by precipitation of the drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. Also the incompatibilities between formulation & gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies.

Centrifugation

Formulations which pass the heating cooling cycle are centrifuged at 3500 r/ min for 30 min. Those formulations that doesn't show any phase separation are taken for the freeze thaw stress test.

Viscosity[12]

The viscosities were measured to determine rheological properties of formulations. Brookfield DV-11+ Pro viscometer at 30˚C with a 62 spindle at 5 rpm was used to serve this purpose.

Globule size measurement[12]

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The emulsion (1-1.5 ml) was transferred to a disposable polystyrene cuvette with the help of plastic syringe or micropipette and the globule size of the emulsion was determined via a combination of laser Doppler velocimetry and phase analysis light scattering (PALS) at an angle of 90°at 25°C.

Poly Dispersity Index (PDI) [12]

PDI value from 0.0 to 0.5 indicates that the uniformity of oil globules is more. So emulsion is more uniform. Poly dispersity index was determined by Malvern Zetasizer Ns90.

Zeta Potential [13-15]

Zeta potential was determined by Malvern Zetasizer NS90. Zeta potential shows an electric charge present on the oil globule. From zeta potential we can conclude that whether emulsion is stable or not. If zeta potential is not reliable then separation occurs in emulsion.

Preparation of Solid Self Microemulsifying Drug Delivery System

The Solid-SMEDDS prepared by lyophilization technique. Mannitol used as the cryoprotectant. Mannitol used in different ratio with liquid SMEDDS to optimize the formulation. The 1%, 1.5%, 2% and 2.5% w/v mannitol (1, 1.5, 2 and 2.5 gm mannitol/ 100 ml liquid SMEDDS) mixed in liquid SMEDDS. The mixture was solidified in lyophilizer at -50 ^{0}C, and Lyophilization was performed at -75°C temperature and 50 mm-Hg vaccum pressure. Prepared lyophilized powder was evaluated.

Evaluation of Solid SMEDDS Formulation

Solid State characterization [15-21]

Micromeritics properties- Study of Angle of repose, Carr's index, Hausner ratio

Drug Content

Required quantity of freeze dried powder equivalent to 20 mg of Olmesartan Medoxomil was diluted with Methanol up to 100 ml. Withdraw 1 ml of above solution and again diluted up to 10 ml with methanol and measured the absorbance at 257 nm using UV spectrophotometer.

Zeta Potential [24]

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Self emulsification time of powder

It was measured by added a water slowly in self-emulsified freeze dried powder and measure the time (sec) until the emulsion was formed.

in Vitro Dissolution Study

In vitro drug release studies from Solid SMEDDS were performed using USP Type I dissolution apparatus with number of paddle rotations set to 50 rpm. The dissolution medium consisted of 900 ml of 0.1N HCL maintained at 37 ±0.5°C. The freeze dried powder containing 20 mg of Olmesartan medoxomil put in capsule and it was introduced into the dissolution medium. At predetermined time intervals 5ml of aliquot was withdrawn, filtered using 0.45µm syringe filter and an equivalent volume of fresh dissolution medium was immediately added. The amount of drug released was estimated by measuring absorbance at 257 nm [23] using a UV spectrophotometer. The dissolution study was carried out with similar procedure as mentioned above for plain drug and marketed tablet with aim of comparison study.

RESULT & DISCUSSION

Evaluation of liquid SMEDDS Formulation

Dispersibility Test

When infinite dilution is done to microemulsion formulation, there is every possibility of it to phase separate leading to precipitation of a poorly soluble drug as microemulsion are formed at a particular concentration of oil, surfactant, co-surfactant and water. For oral microemulsions the process of dilution by the GI fluids will result in the gradual desorption of surfactant located at the globule interface. The process is thermodynamically driven by the requirement of the surfactant to maintain an aqueous phase concentration equivalent to its CMC. In the present study, we used distilled water and 0.1 N HCl as a dispersion medium because it is well reported that there is no significant difference in the microemulsions prepared using nonionic surfactants, dispersed in either water or simulated gastric or intestinal fluid. Formulations that passed Dispersibility test in Grade A and B were taken for further study, as Grade A and B formulations will remain as microemulsions when dispersed in GIT. All the formulation that were falling in Grade C and D of Dispersibility tests were discarded for further study.

Robustness on dilution

The prepared formulation diluated when 100 times with distilled water and 0.1 N HCL were found to be stable without any precipitation.

Emulsification Time

Self-emulsification time was measured using stop watch. It was measure by adding water in liquid SMEDDS and measured time for formed an emulsion. The formulation B_{12} has less self-emulsification time was found to be 18±2.64 second as compared as other formulation.

% Transmittance

The clarity of microemulsions was checked by transparency, measured in terms of transmittance (%T). SMEDDS forms o/w microemulsion since water is external phase. Formulation B_{12} has % transmittance value greater than 99%.These results indicate the high clarity of microemulsion. In case of other systems %T values were about 80% suggesting less clarity of microemulsions. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T.

Drug Content

Drug content was measured using UV spectrophotometer at 257 nm. Drug content was measured using linearity equation of methanol. The formulation B_{12} has maximum drug content of liquid SMEDDS was found to be 99±0.009 % of optimized batch.

In vitro drug release

Dissolution studies were performed for the SMEDDS formulations in 0.1 N HCL. The maximum drug release of batch no B_{12} was 99.43±0.015 % within the 45 min in case of SMEDDS.

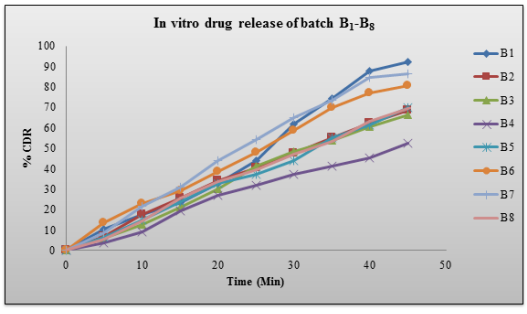

FIGURE 1: In vitro drug release of batch B^1 to B^8

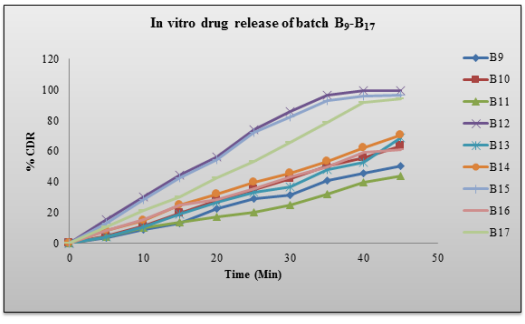

FIGURE 2: In vitro drug release of batch B^9 to B^{17}

Thermodynamic stability studies

Microemulsions are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant, co-surfactant and water, with no phase separation, creaming or cracking. It is the thermo stability which differentiates nano or micro emulsion from emulsions that have kinetic stability and will eventually phase separator. Thus, the selected formulations were subjected to different thermodynamic stability by using heating cooling cycle, centrifugation and freeze thaw cycle stress tests. Those formulations, which survived thermodynamic stability tests, were taken for further study.

Viscosity

TABLE 1: Viscosity of optimize SMEDDS formulation

Batch No	Viscosity (cp)
B_1	0.8872
B_2	0.9176
B_3	0.9244
B_4	0.9277

The viscosity of microemulsion systems can be monitored by standard rheological techniques. It depends on oils and Smix used. It was observed that the viscosity of all the formulations is less than 0.9277 cP. Formulation, B1 has the minimum viscosity 0.8872 cP which is highly similar to that of water i.e.1.0. Thus, it shows that SMEDDS forms o/w microemulsion water remains as external phase and viscosity of SMEDDS is near to water. This reveals that formulation B12 is very clear, transparent and low viscous liquid.

Globule size measurement

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The globules size of optimized batch B12 was found to be 92.28 nm.

TABLE 2: Globule size of optimize SMEDDS formulation

Batch No	Globule size (nm)
B_1	92.28
B_2	124.8
B_3	170.2
B_4	284.1

Poly Dispersity Index (PDI)

Poly dispersity index of the emulsion was measured by Malvern Zetasizer NS90. PDI of optimized batch B1 was found to be 0.243.

TABLE 3: Poly Dispersity Index of optimize SMEDDS formulation

Batch No	Poly Dispersity Index
B_1	0.243
B_2	0.333
B_3	0.418
B_4	0.484

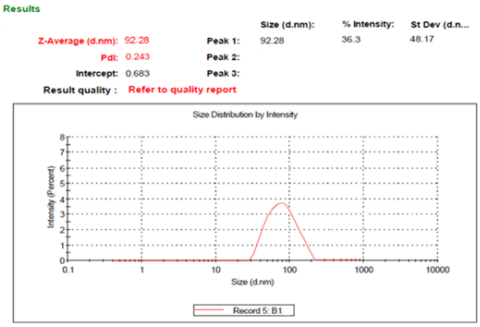

FIGURE 3: Droplet size and PDI of Batch B1

Zeta potential

Zeta potential was determined by Malvern Zetasizer NS90. Zeta potential shows an electric charge present on the oil globule. Zeta potential of optimized batch B1 was found to be -27.5 mv.

TABLE 4: Zeta potential of optimize SMEDDS formulation

Batch No	Zeta potential (mv)
B_1	-27.5
B_2	-22.9
B_3	-16.0
B_4	-14.4

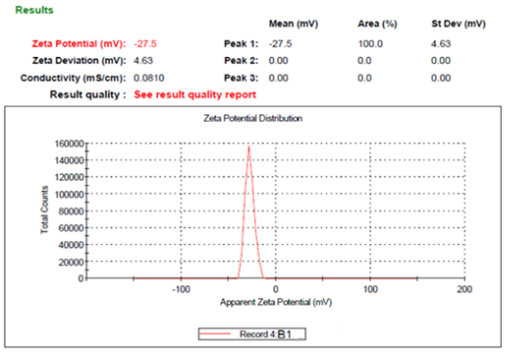

FIGURE 4: Zeta potential of batch B_{12}

DISCUSSION

Globule size, poly dispersity index and Zeta potential of batch A1 is the best than the other batches. Poly dispersity index was 0.243, so we can say that batch A1had more uniformity than other batches. Size of oil globules is 92.28 nm. So we can say that globule size was small as micro emulsion. The zeta potential was -27.5 mv. So we can say that emulsion was stable and having very less charge on oil globule.

Preparation of Solid SMEDDS Formulation

The solid-SMEDDS was prepared by using different ratio of mannitol. The mannitol used in 1%, 1.5%, 2% and 2.5 % w/v ratio with liquid SMEDDS. Then this mixture was lyophilized. This freeze dried powder was analyzed. This freeze dried powder with different ratio of mannitol, the 2% w/v of mannitol has a good efficiency to convert the liquid SMEDDS to solid-SMEDDS as compared to other ratio of mannitol. So 2% w/v ratio of mannitol to further analyzed.

Evaluation of Solid SMEDDS Formulation

Solid State characterization

Bulk density of optimized freeze dried powder was measured by direct filling of self-emulsified freeze dried powder in measuring cylinder. Bulk density was found to be 0.59±0.012. Tapped density was found to be 0.68±003. Carr's Index and Hausner's of optimized freeze dried powder was measured of self-emulsified freeze dried powder was found to be 14.80±2.76 and 1.14±0.03 respectively. Angle of repose of optimized freeze dried powder was found to be 24.91±1.25°.

Characterization of Solid SMEDDS Formulation

Drug Content

Drug content was measured using UV spectrophotometer at 257 nm. Drug content was measured using linearity equation of methanol. The drug content of self emulsified freeze dried powder was found to be 96.15±0.15% of optimized batch.

Zeta Potential

Zeta potential was determined by Malvern Zetasizer NS90. Zeta potential shows an electric charge present on the oil globule. Zeta potential of optimized freeze dried powder was found to be -22.5 mv.

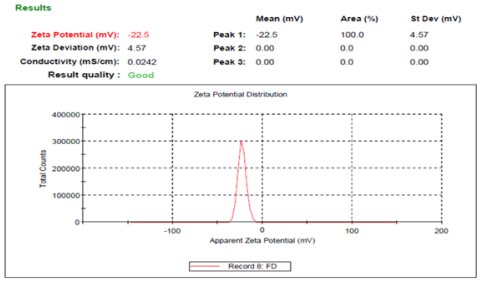

FIGURE 5: Zeta potential of Freeze Dried Powder

Globule Size

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The globules size of optimized freeze dried powder was found to be 98.24 nm.

Self emulsification time of powder

Self-emulsification time was measured using stop watch. It was measure by adding water in self-emulsified freeze dried powder and measured time for formed an emulsion. The self-emulsification time was found to be 20±3.60 second.

Poly Disperbility Index

Poly dispersity index of the emulsion was measured by Malvern Zetasizer NS90. PDI of optimized freeze dried powder was found to be 0.304.

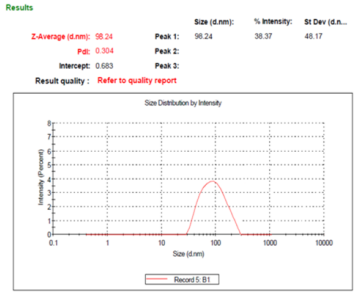

FIGURE 6: Droplet size and PDI of Freeze Dried Powder

In vitro Drug release

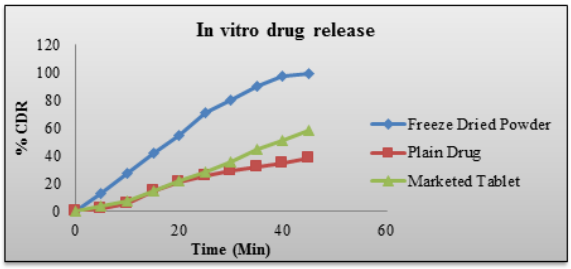

FIGURE 7: Invitro drug release of freeze dried powder, Plain drug & Marketed Tablet

Dissolution studies were performed for the Solid-SMEDDS freeze dried powder in 0.1 N HCL There is about 99.28±0.013% of the drug is released within 45 min in freeze dried Solid-SMEDDS, while plain drug showed only 37.88±0.025 % and marketed formulation showed only 58.31±0.015 % dissolution at the end of 45 min. The *in vitro* dissolution studies indicate that formulation of OLM in the form of freeze dried powder of SMEDDS enhances the dissolution properties.

CONCLUSION

The SMEDDS formulations were evaluated, the batch B_1, B_2, B_3 and B_4 has a disperbility grade A expects other batches. According to the robustness on dilution study all batches are be stable without any precipitation diluated when 100 times with distilled water and 0.1 N HCL. The highest amount of drug content of batch B_1 was found to be 99±0.009 %. The maximum drug release of batch no B_1 was 99.43±0.015 % within the 45 min in case of SMEDDS. The batch B_1, B_2, B_3 and $B_4$was passed the thermodynamic stability while other batch failed the thermodynamic stability. According to thermodynamic stability passed 4 batches was evaluated for the zeta potential, globule size, poly disperbility index and viscosity. These 4 batches were tested in malvern zetasizer NS90 the batch B_1 has best result compare to other 3 batches. The zeta potential droplet size, globule size and poly disperbility index of batch B_{12} was found to be -27.5 mv, 98.28 nm and 0.243 respectively**.** The solid-SMEDDS formulation prepared by lyophilization technique. Mannitol used as cryoprotectant for the solid-SMEDDS formulation. The composition of batch OLM 20 mg, Oil 1 ml, surfactant 2.5 ml co-surfactant 4.5 ml and mannitol used in different ratio for preparation of solid-SMEDDS. The mannitol 2% w/v mannitol used as cryoprotectant gives the best result. The solid state characteristics of freeze dried powder bulk density, tapped density, carr's index, hausner's ratio and angle of repose was found to be 0.59±0.012, 0.68±0.03, 14.80±2.76, 1.14±0.03 and 24.91±1.25° respectively. The drug content of freeze dried powder was found to be 96.15±0.15%. The emulsification time of freeze dried powder was found to be 20±3.60 sec. The zeta potential, droplet size and poly disperbility index of freeze dried powder was found to be - 22.5 mv, 98.4 nm and 0.304 respectively**.** The cumulative drug release of freeze dried powder within 45 min was found to be 99.28±0.013%, while plain drug showed only 37.88±0.025 % and marketed formulation showed only 58.31±0.015 % dissolution at the end of 45 min.

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